Optimal Duration of DAPT after DES:
6 Months is Enough

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DJC-TCT AP 2015: 12 mins

Disclosures

Grant Support/Drugs

- Daiichi-Sankyo - Eli Lilly
- Astra-Zeneca - Merck

Grant Support/Devices

- Edwards Lifesciences - Abbott Vascular
- Medtronic - Boston Scientific
- Biomet - Covidien

Consulting/Advisory Boards

- Medtronic - Astra-Zeneca
- Eli Lilly

DJC: 2/15

More Important Disclosures

- I am a member of the steering committee of the DAPT trial and have co-authored several of the major publications of the trial. Not surprisingly, I happen to think that DAPT was an exceptionally well-done trial
- Like any good debater, however, I am willing and able to defend either side of a good argument

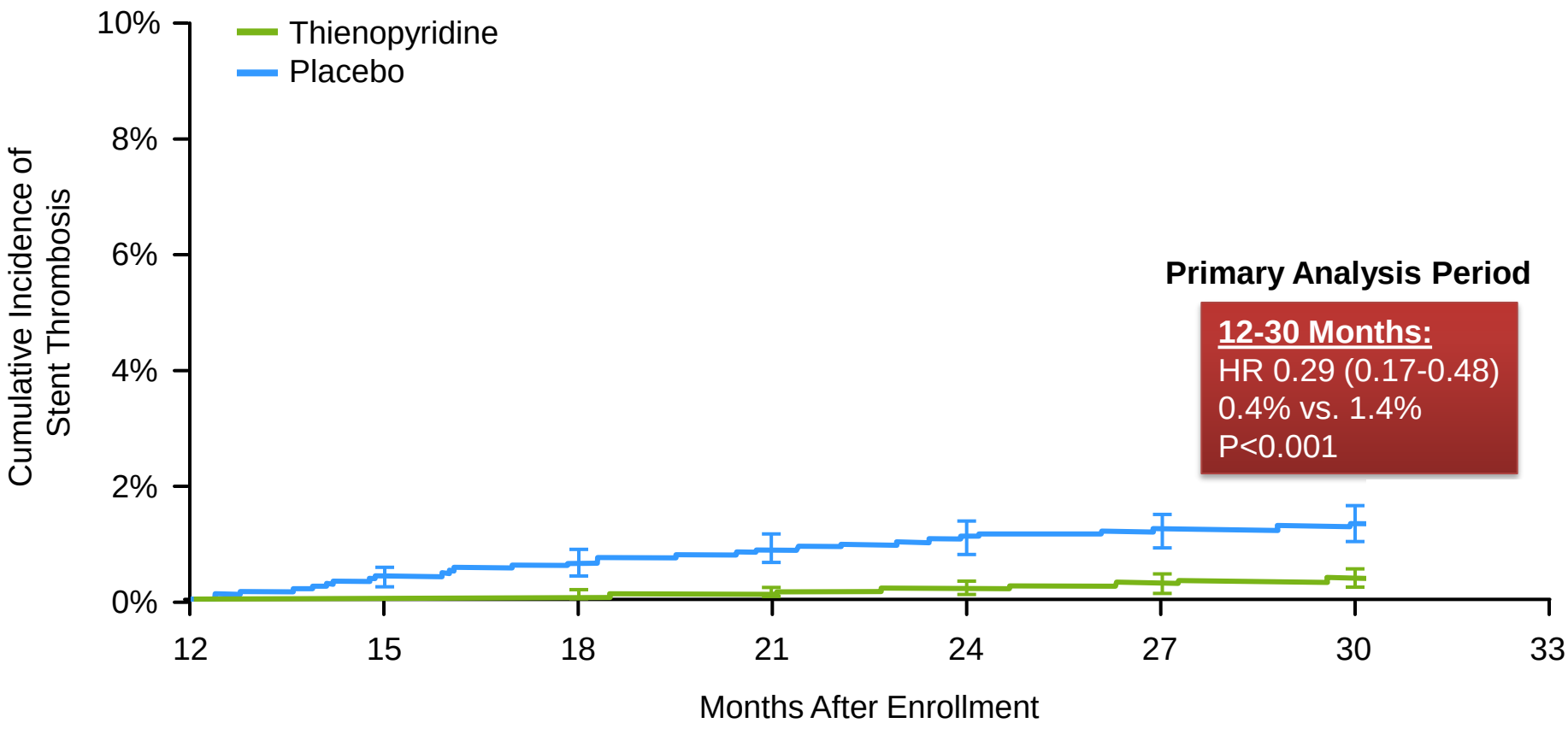
Origins of the Controversy

- DAPT is currently recommended for 6 months (EU) to 1 year (US) after DES implantation
- Some observational studies have suggested that extending DAPT beyond 1 year is associated with a lower risk of MI, but at the price of increased risk of bleeding
- Several modest sized RCTs (ZEST, PRODIGY) have failed to demonstrate a benefit of prolonged DAPT, however
- The DAPT trial was designed (in late 2006, at the height of the “DES firestorm”) to determine the benefits and risks of continuing DAPT beyond 1 year after DES implantation

DAPT: Methods

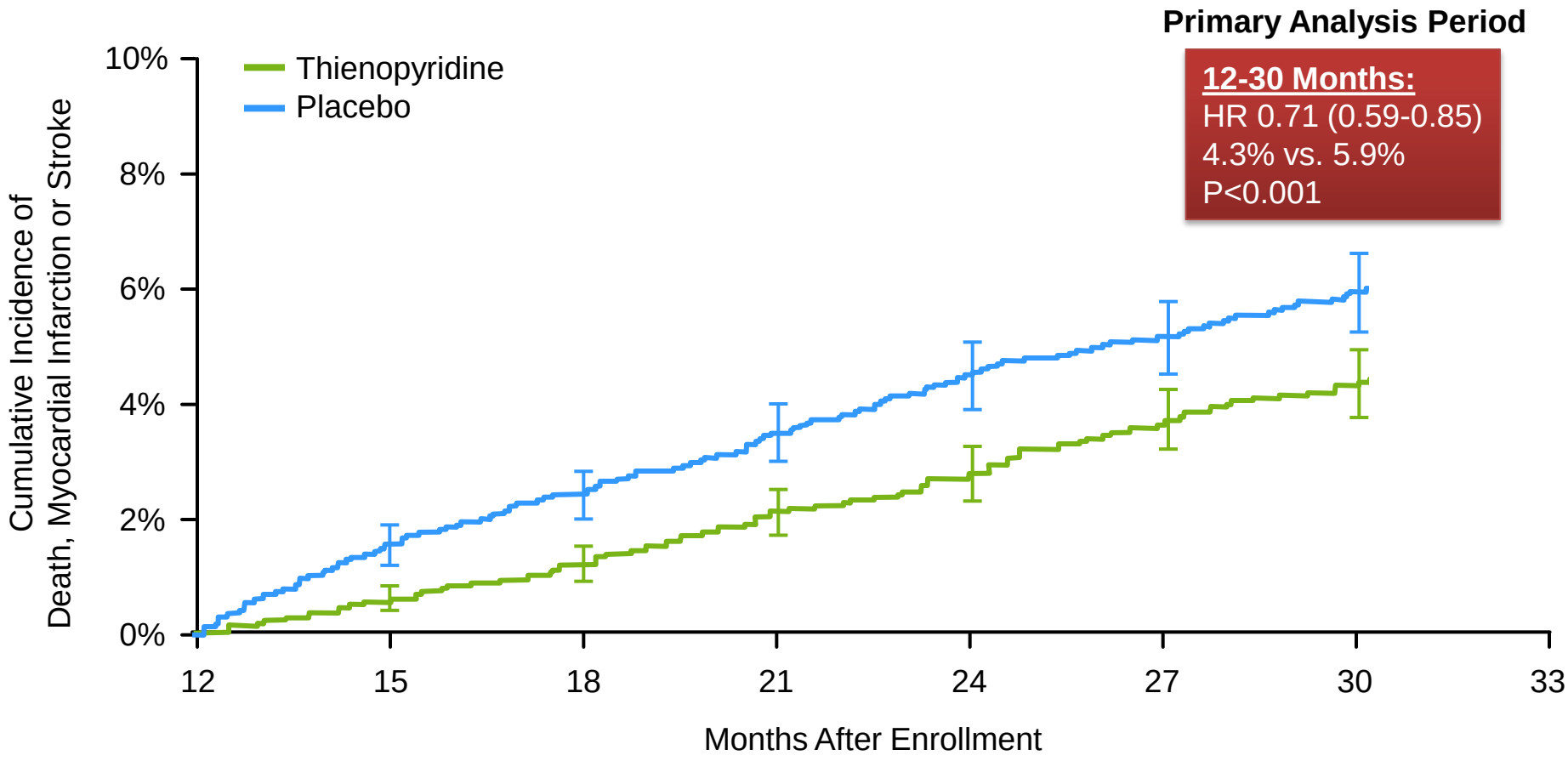
- 9,961 pts who remained event-free 12 months after DES randomized to receive ASA + thienopyridine (clopidogrel or prasugrel) vs. ASA + placebo for an additional 18 months (12 vs. 30 month DAPT)
- Co-Primary Efficacy Endpoints
  - *Stent Thrombosis*
  - *MACCE (composite of death, MI, or stroke)*
- Primary Safety Endpoint: Moderate/severe bleeding
- Both first, second, and third generation DES used in trial (sirolimus, paclitaxel, zotarolimus, and everolimus)

Co-Primary Effectiveness End Point
Stent Thrombosis



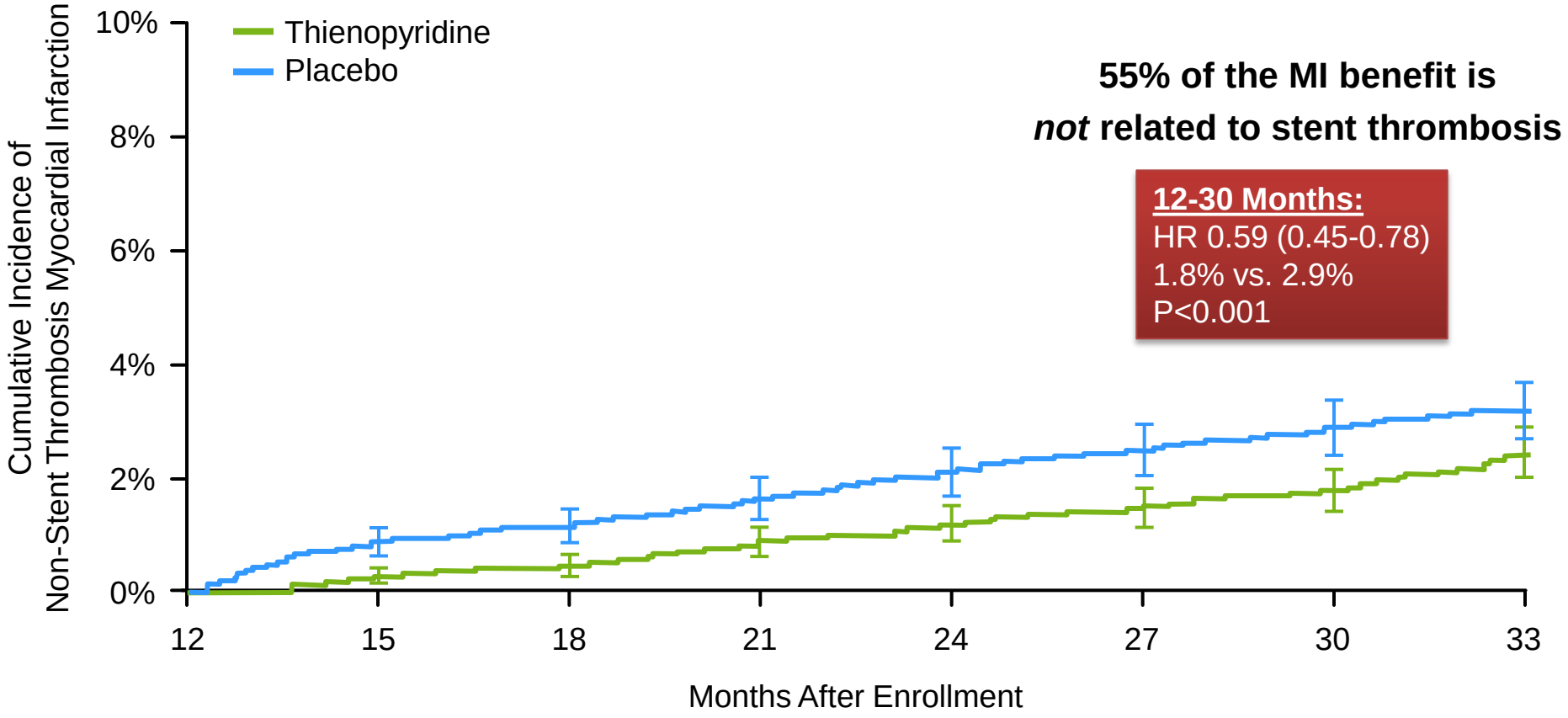
# At Risk								
Thienopyridine	5020	4934	4870	4828	4765	4686	4642	3110
Placebo	4941	4845	4775	4721	4651	4603	4556	3105

Co-Primary Effectiveness End Point MACCE



# At Risk								
Thienopyridine	5020	4917	4840	4778	4702	4611	4554	3029
Placebo	4941	4799	4715	4635	4542	4476	4412	2997

Non-Stent Thrombosis Myocardial Infarction

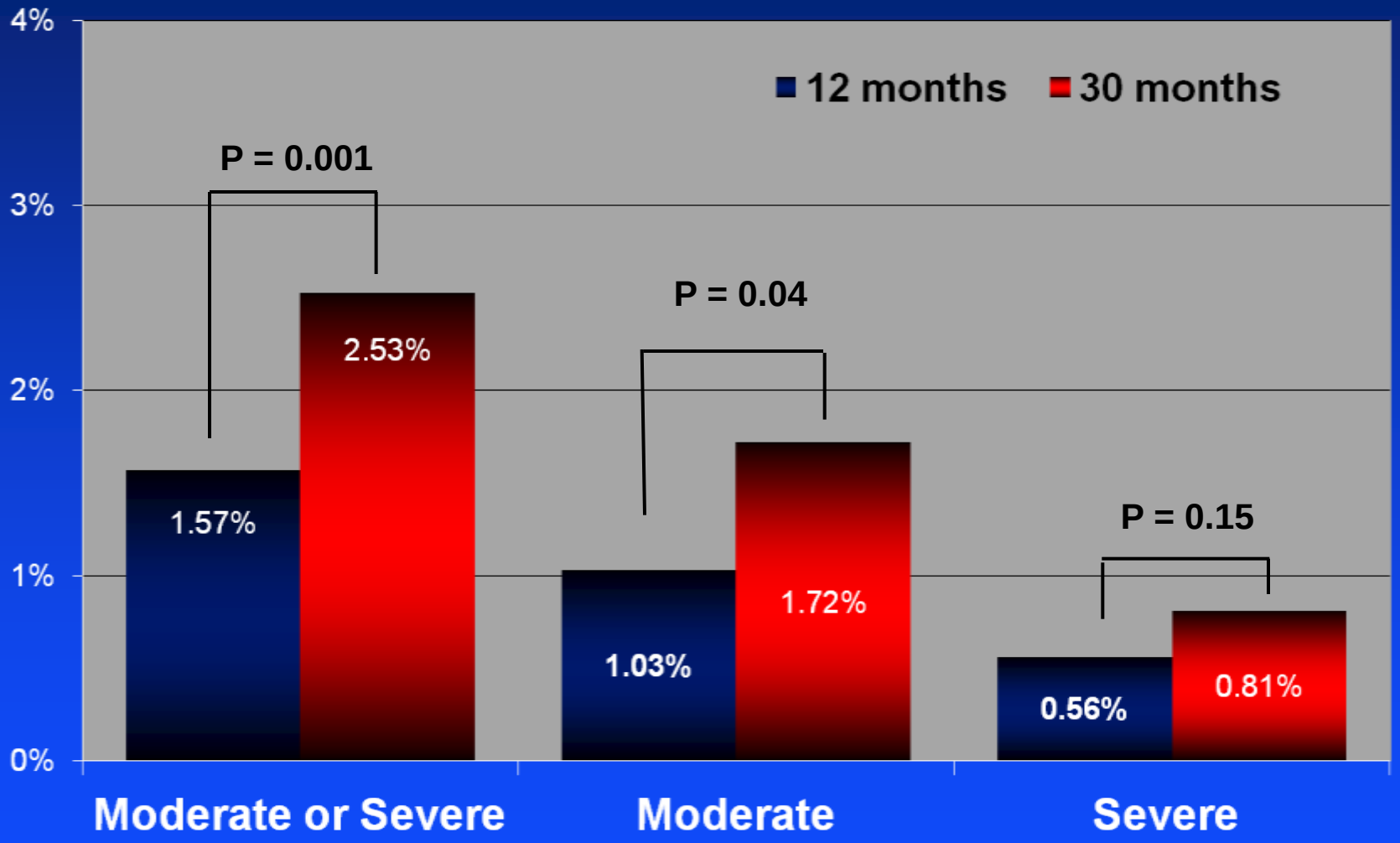


55% of the MI benefit is *not* related to stent thrombosis

12-30 Months:
HR 0.59 (0.45-0.78)
1.8% vs. 2.9%
P<0.001

# At Risk								
Thienopyridine	5020	4920	4851	4792	4721	4641	4588	3066
Placebo	4941	4820	4751	4686	4607	4547	4491	3052

DAPT: GUSTO Bleeding



Let's start with some concessions…

- The DAPT trial was an exceptionally well-done trial
- The DAPT trial has shown conclusively that longer term DAPT reduces rates of stent thrombosis and MACE (death/MI/stroke) compared with shorter term DAPT
- The DAPT trial also showed convincingly that prolonged DAPT after DES is associated with an increased risk of major bleeding (although fatal bleeding was not increased)

Rationale for 6 months of DAPT

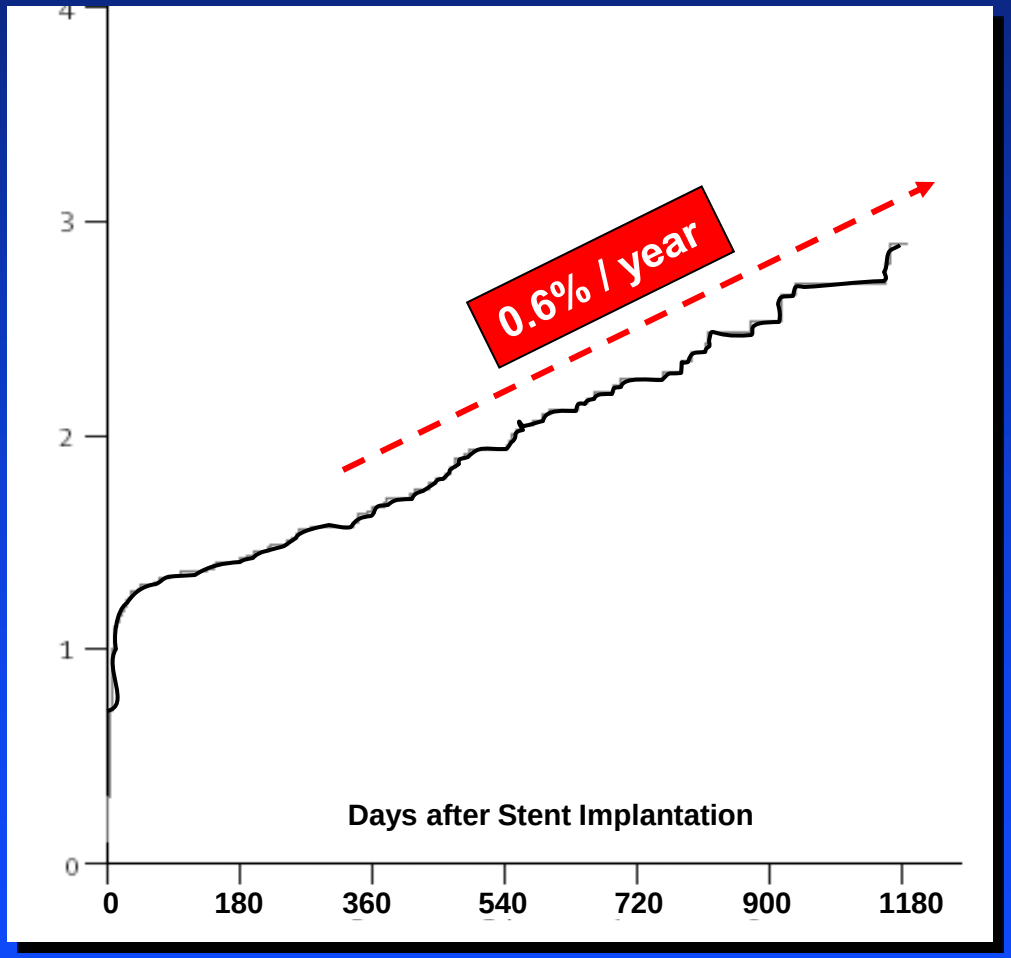
Biologic Considerations

Key Observations

- Very late stent thrombosis was mainly an issue with 1st generation DES (esp. TAXUS)
- Widespread adoption of 2nd generation DES has substantially altered the risk-benefit equation in favor of shorter term DAPT

Stent Thrombosis in the “Real World”

Definite Stent Thrombosis (%)

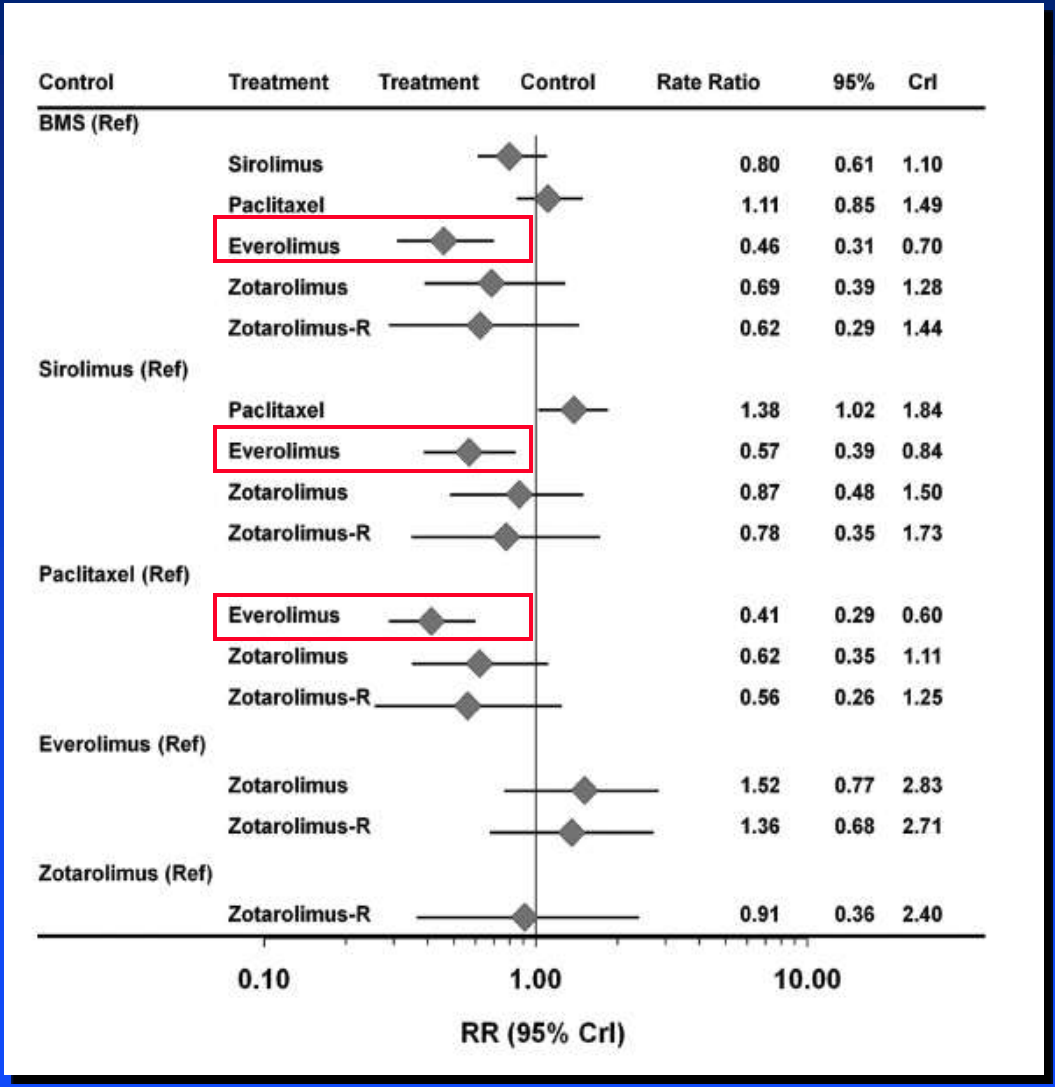


Bern/Rotterdam Study

- 8146 unselected pts treated with DES
  - 47% SES; 53% PES
- 152 documented cases of stent thrombosis
- Median time to ST = 9 days
- Beyond 30 days, stent thrombosis occurred at a constant rate of 6 per 1000 patient-years

Daemen J et al. Lancet 2007;369:667-78

DES vs. BMS Meta-Analysis: Stent Thrombosis

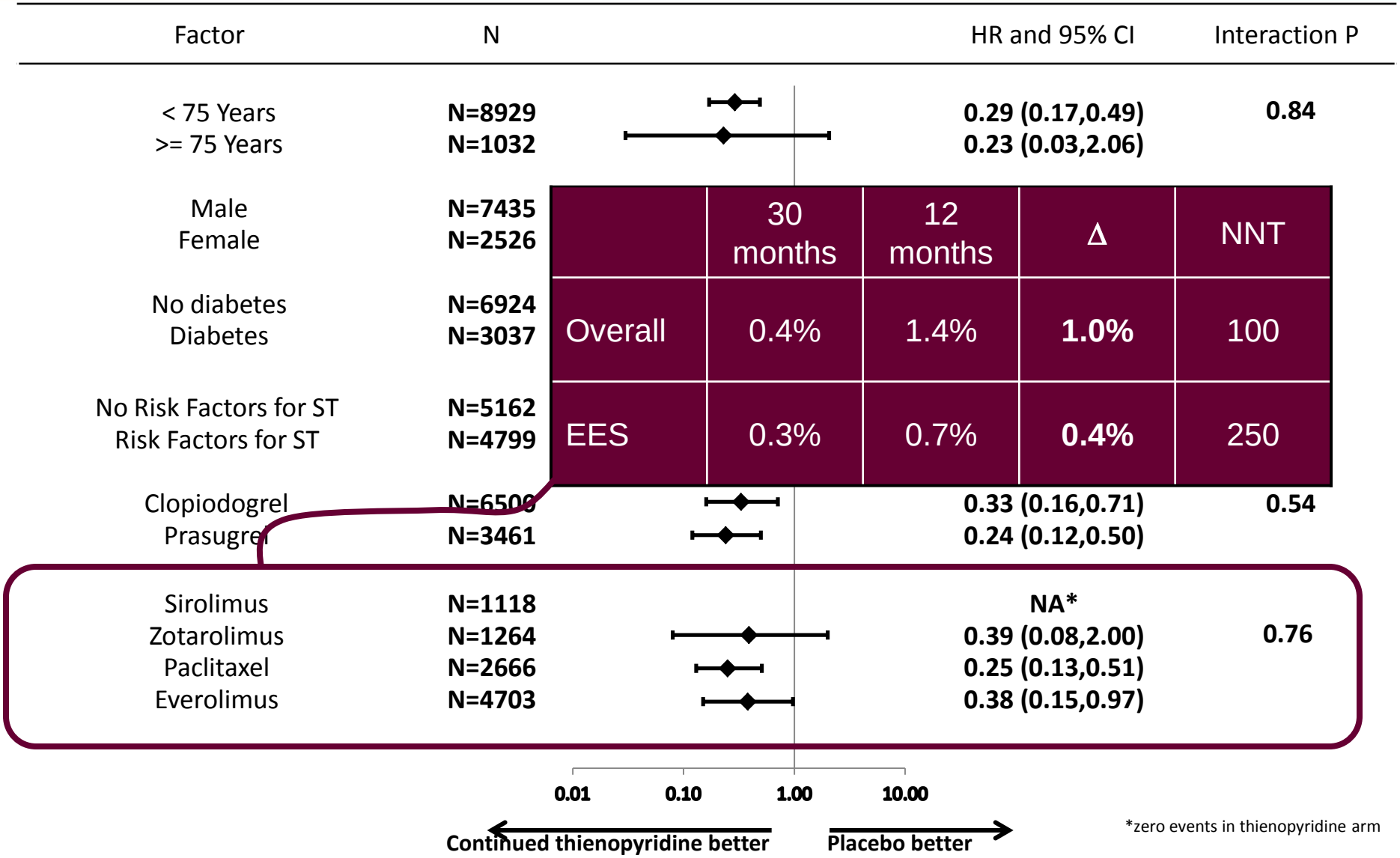


Network Meta-Analysis

- 77 RCTs involving 57,138 patients
- EES associated with lower rate of long-term stent thrombosis than BMS, PES, and, SES
- Results confirmed in more recent analyses extending f/u to 4 years

Bangalore S et al. Circulation 2012;125:2873-91

Consistency of Treatment Effect Stent Thrombosis (12-30 Months)



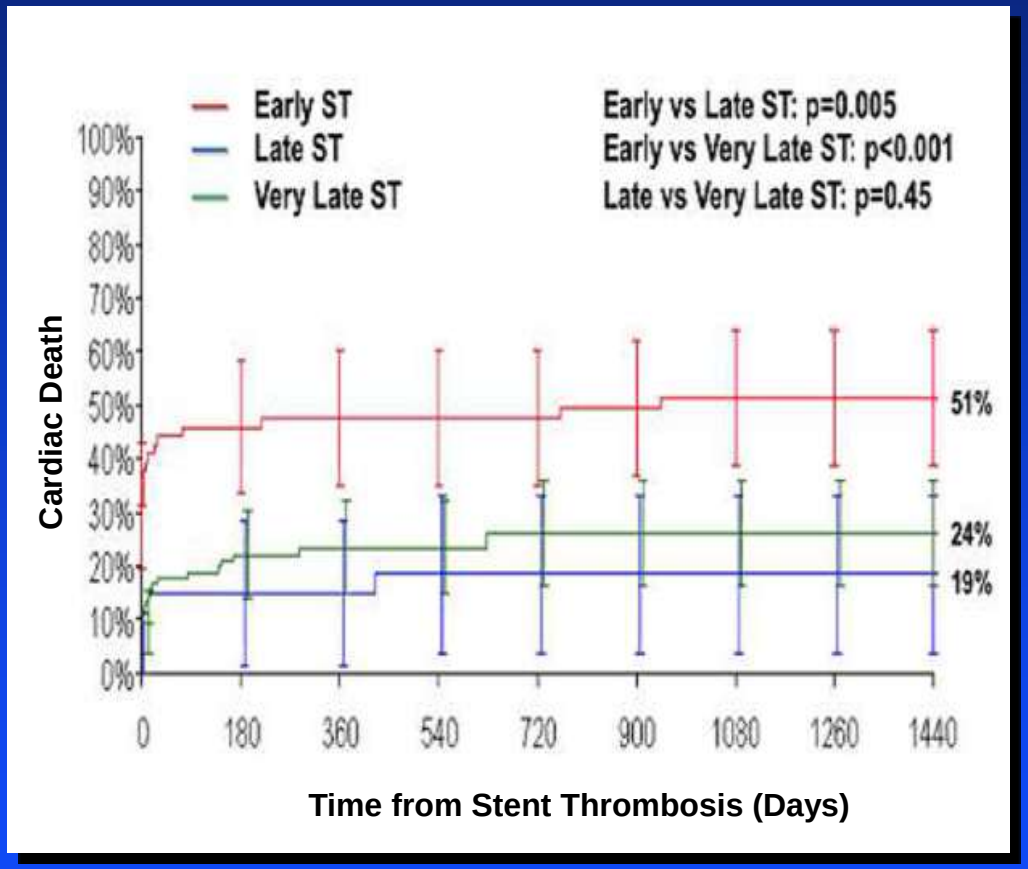
Rationale for 6 months of DAPT

Risk-Benefit Balance

Key Observations

- VLST appears to be biologically different from acute/subacute stent thrombosis– both in terms of biology and prognosis
- Bleeding is bad → potentially as prognostically important as late MI

Differential Outcomes of Early vs. Late ST

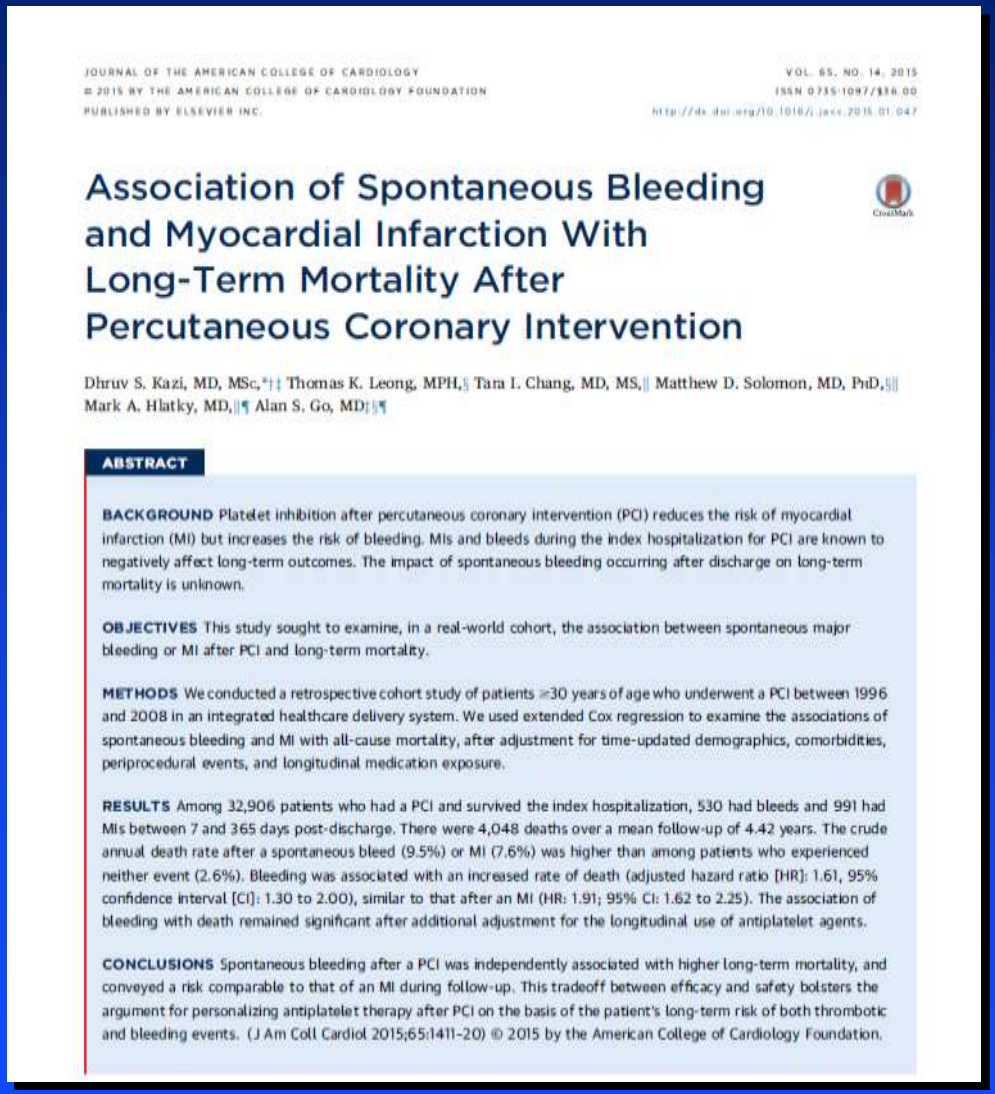


PROTECT Trial Substudy

- Definite ST occurred in 184 patients over 4 years (61 early, 27 late, 96 very late)
- Both LST and VLST independently associated with ↓'d long-term mortality vs. early ST
- Similar results seen in several additional studies (Wenaweser JACC 2008, Armstron JACC Int 2012)

Secemsky EA, et al. AJC 2015 (in press)

Prognostic Importance of Late Bleeding



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Association of Spontaneous Bleeding and Myocardial Infarction With Long-Term Mortality After Percutaneous Coronary Intervention

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ABSTRACT

BACKGROUND Platelet inhibition after percutaneous coronary intervention (PCI) reduces the risk of myocardial infarction (MI) but increases the risk of bleeding. MIs and bleeds during the index hospitalization for PCI are known to negatively affect long-term outcomes. The impact of spontaneous bleeding occurring after discharge on long-term mortality is unknown.

OBJECTIVES This study sought to examine, in a real-world cohort, the association between spontaneous major bleeding or MI after PCI and long-term mortality.

METHODS We conducted a retrospective cohort study of patients ≥30 years of age who underwent a PCI between 1996 and 2008 in an integrated healthcare delivery system. We used extended Cox regression to examine the associations of spontaneous bleeding and MI with all-cause mortality, after adjustment for time-updated demographics, comorbidities, periprocedural events, and longitudinal medication exposure.

RESULTS Among 32,906 patients who had a PCI and survived the index hospitalization, 530 had bleeds and 991 had MIs between 7 and 365 days post-discharge. There were 4,048 deaths over a mean follow-up of 4.42 years. The crude annual death rate after a spontaneous bleed (9.5%) or MI (7.6%) was higher than among patients who experienced neither event (2.6%). Bleeding was associated with an increased rate of death (adjusted hazard ratio [HR]: 1.61, 95% confidence interval [CI]: 1.30 to 2.00), similar to that after an MI (HR: 1.91; 95% CI: 1.62 to 2.25). The association of bleeding with death remained significant after additional adjustment for the longitudinal use of antiplatelet agents.

CONCLUSIONS Spontaneous bleeding after a PCI was independently associated with higher long-term mortality, and conveyed a risk comparable to that of an MI during follow-up. This tradeoff between efficacy and safety bolsters the argument for personalizing antiplatelet therapy after PCI on the basis of the patient's long-term risk of both thrombotic and bleeding events. (J Am Coll Cardiol 2015;65:1411–20) © 2015 by the American College of Cardiology Foundation.

Kaiser Study

- 32,906 PCI patients followed for a median of 4.4 yrs
- Time-varying Cox models used to adjust for multiple covariates both at baseline and during follow-up

Adjusted HRs for mortality:

- Spontaneous Bleed 1.61
- Spontaneous MI: 1.91

Khazi DS, et al. J Am Coll Cardiol 2015;65:1411-20

Is the Prognostic Impact of Bleeding Real?

Intervention	RCT(s)	Population	Mortality
Bivalirudin	• HORIZONS-AMI • MATRIX	STEMI or NSTEMI with PCI	↓
Fondaparinux	• OASIS-V	STEMI or NSTEMI	↓
Transradial PCI	• RIVAL • RIFLE • MATRIX	STEMI or NSTEMI with PCI	↓

Let's do the math….

- For every patient treated with a 2nd gen DES, extension of DAPT from 12 to 30 months leads to:
  - *↓VLST from 0.7% to 0.3% (NNT = 250)*
  - *↓reduction in MI (including ST-related events) from 3.2% to 2.1% (NNT = 91)*
  - *↑moderate/severe bleeding from 1.3% to 2.5% (NNH = 83)*

Bottom Line

- For every late MI prevented, we will cause 1.1 GUSTO moderate or severe bleeds
- For every VLST prevented, we will cause 3 bleeds

Rationale for 6 months of DAPT

Statistical and EBM Considerations

Key Observations

- Pooled data from trials of short vs. long-term DAPT after DES suggest that prolonged DAPT may do more harm than good

Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials

Tullio Palmerini, Umberto Benedetto, Letizia Bacchi-Reggiani, Diego Della Riva, Giuseppe Biondi-Zoccai, Fausto Feres, Alexandre Abizaid, Myeong-Ki Hong, Byeong-Keuk Kim, Yangsoo Jang, Hyo-Soo Kim, Kyung Woo Park, Philippe Genereux, Deepak L Bhatt, Carlotta Orlandi, Stefano De Servi, Mario Petrou, Claudio Rapezzi, Gregg W Stone

Summary

Background Despite recent studies, the optimum duration of dual antiplatelet therapy (DAPT) after coronary drug-eluting stent placement remains uncertain. We performed a meta-analysis with several analytical approaches to investigate mortality and other clinical outcomes with different DAPT strategies.

Methods We searched Medline, Embase, Cochrane databases, and proceedings of international meetings on Nov 20, 2014, for randomised controlled trials comparing different DAPT durations after drug-eluting stent implantation. We extracted study design, inclusion and exclusion criteria, sample characteristics, and clinical outcomes. DAPT duration was categorised in each study as shorter versus longer, and as 6 months or shorter versus 1 year versus longer than 1 year. Analyses were done by both frequentist and Bayesian approaches.

Findings We identified ten trials published between Dec 16, 2011, and Nov 16, 2014, including 31 666 randomly assigned patients. By frequentist pairwise meta-analysis, shorter DAPT was associated with significantly lower all-cause mortality compared with longer DAPT (HR 0·82, 95% CI 0·69–0·98; p=0·02; number needed to treat [NNT]=325), with no significant heterogeneity apparent across trials. The reduced mortality with shorter compared with longer DAPT was attributable to lower non-cardiac mortality (0·67, 0·51–0·89; p=0·006; NNT=347), with similar cardiac mortality (0·93, 0·73–1·17; p=0.52). Shorter DAPT was also associated with a lower risk of major bleeding, but a higher risk of myocardial infarction and stent thrombosis. We noted similar results in a Bayesian framework with non-informative priors. By network meta-analysis, patients treated with 6-month or shorter DAPT and 1-year DAPT had higher risk of myocardial infarction and stent thrombosis but lower risk of mortality compared with patients treated with DAPT for longer than 1 year. Patients treated with DAPT for 6 months or shorter had similar rates of mortality, myocardial infarction, and stent thrombosis, but lower rates of major bleeding than did patients treated with 1-year DAPT.

Interpretation Although treatment with DAPT beyond 1 year after drug-eluting stent implantation reduces myocardial infarction and stent thrombosis, it is associated with increased mortality because of an increased risk of non-cardiovascular mortality not offset by a reduction in cardiac mortality.

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Palmerini T, et al. Lancet 2015

Mortality: Short vs. Long DAPT

Death (All-Cause)

HR (95% CI)

Study

ARCTIC-I

DAPT, 20

DES-LATE

EXCELLEN

ISAR-SAF

ITALIC, 2

OPTIMIZE

PRODIGY

RESET, 2

SECURITY

I-V: (I^2=0

D+L: p va

Cardiac Death

HR (95% CI)

Study

DAPT,

DES-LA

EXCELL

ITALIC,

OPTIM

PRODI

RESET,

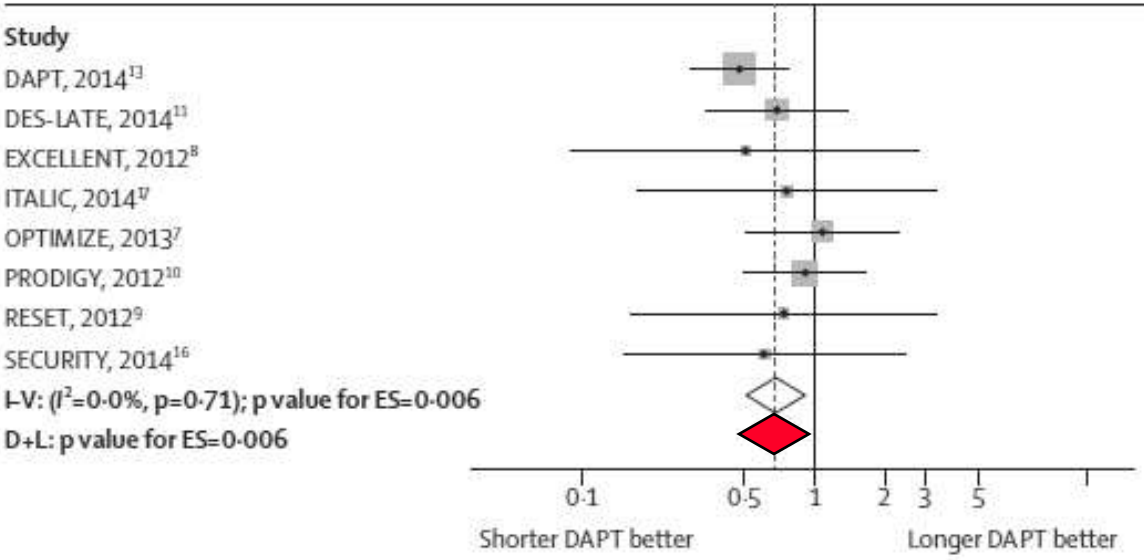
SECURI

I-V: (I^2=

D+L: p

Non-cardiac Death

HR (95% CI)



Palmerini T, et al. Lancet 2015

Summary

- For patients treated with current generation DES, evidence would suggest that a 3-6 month period of DAPT is “mandatory” for avoidance of the most seere and prognostically important stent-related complications
- Although it is clear that longer-term DAPT can prevent additional stent thrombosis events (as well as non-stent related events), there is a definite price to be paid for these benefits in terms of increased bleeding

Conclusions

- Given the importance of late bleeding events in terms of cost, QOL, and (potentially) long-term mortality as well as the lack of definitive survival benefit with more prolonged DAPT, it makes senses to individualize the duration of DAPT beyond 6 months – taking into account factors such as extent of CAD and vascular disease, as well as long-term bleeding risk
- Ongoing work in the DAPT trial and other studies should help to clarify the balance of ischemic vs. bleeding risk for individual patients